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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,685	09/19/2005	Eva Caroff	66535.000004	7434

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EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1617	

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06/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,685	CAROFF ET AL.	
	Examiner	Art Unit	
	SARAH PIHONAK	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-16 and 22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,13,14 and 22-26* is/are rejected.

7)☐ Claim(s) *12,15 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 (national stage application) of PCT/CH04/00175, filed on 3/22/2004.

Priority

This application, filed on 9/19/2005, claims foreign priority to CH 466/03, which was filed on 3/20/2003. The foreign application provides support to the instant claims. Therefore, the priority date given to the instant claims is 3/20/2003, and the effective U.S. filing date is 3/22/2004, which was the filing date of the PCT.

Response to Arguments

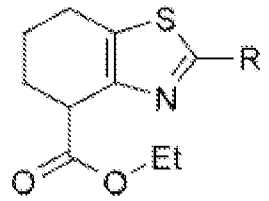
1. Previously, claims 1-21 were pending. In the office action dated 10/28/2008, claims 8-11, 17-18 were examined for patentability. Claims 1-7, 12-16, and 19-21 were withdrawn from consideration as being directed to non-elected inventions and species. In the reply filed on 3/2/2009, the Applicants cancelled claims 1-10 and 17-21, and added new claims 22-26.

2. In the office action dated 10/28/2008, claims 8-11, and 17-18 were rejected under 35 USC § 112, second paragraph, for indefiniteness. The rejection of claims 8-10 and 17-18 is considered moot as these claims have been cancelled. The Applicants have amended claim 11 to incorporate the structure of formula I and to remove vagueness associated with the claim; therefore, the rejection of claim 11 under 35 USC § 112, second paragraph, is withdrawn. In the earlier mailed office action, claims 8-11, and 17-18 had been rejected under 35 USC § 112, first paragraph, as the claims had

cited solvates of formula I. The rejection of claims 8-10 and 17-18 under this statute is considered moot, as these claims have been cancelled. The discussion of this rejection will be limited to claim 11. The Applicants argued that the specification does enable making solvates of formula I, as the specification is enabling for making salts of formula I. This argument has been fully considered but is not found persuasive. In the office action dated 10/28/2008, the examiner had cited the reference of West, "Solid State Chemistry and its Applications", Wiley, New York, 1988, pp. 358, 365. In particular, West states "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent" (p. 365). West also defines a solvate of an organic compound as a species in which a solvent molecule is introduced into the crystal (p. 358, 2nd paragraph). As the prior art provides evidence that it is not possible to readily predict whether solvates of a compound will form, or what their stoichiometric formula will be, without detailed experimentation, the instant specification is not enabling for making all possible solvates of formula I. As such, rejection of claim 11 under 35 USC § 112, first paragraph was considered proper. However, it is noted that claim 11 has been amended by the Applicants as an independent claim, which no longer incorporates the broad term 'solvates'. Therefore, the rejection of instant claim 11 under 35 USC § 112, first paragraph has been withdrawn due to the claim amendment.

3. Applicant's arguments filed 3/2/2009 have been fully considered but they are not found persuasive, regarding the rejection of claims 8-11 under 35 USC § 102, as being anticipated by Marinko et. al.,Tetrahedron Lett., 42, pp. 8911-8913. The rejection of claims 8-10 is considered moot as the claims have been cancelled. The Applicants

traversal regarding the rejection of claim 11 is addressed. The Applicants argued that Marinko et. al. does not anticipate the compound of instant claim 11, as the structure that Marinko et. al. discloses has a different substituent on the ring structure than those cited in claim 11. The structure taught by Marinko et. al. is shown below (p. 8912, Scheme 1, structure 6b):

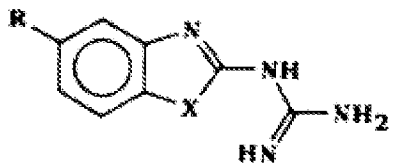


Where R=NHC(NH)NH_2

The ring structure of the compound taught by Marinko et. al. has an ethoxycarbonyl substituent. The core ring structure of the compound taught by Marinko et. al. and the instant claim is the same. The Applicants have argued that instant claim 11 does not cite ethoxycarbonyl substituents. However, it is noted that this argument applies to the amended claim 11, and not the previous set of claims that had been referenced in the previous office action dated 10/28/2008. It is particularly noted that, prior to amendment, claim 11 had cited the core structure of formula I (of claim1, prior to amendment), in which the ring substituent(s) are selected from a list of groups, which included ethoxycarbonyl groups. Therefore, Marinko et. al. did anticipate the compound cited in the previous claim 11, and the rejection of this claim under 35 USC § 102(b) was proper. However, along with the submitted response to the office action, the Applicants amended claim 11 to remove 'ethoxycarbonyl' substituents from the claim. Therefore,

the rejection of instant claim 11 under 35 USC § 102(b) over Marinko et. al. is withdrawn due to the amendment.

4. Applicant's arguments, filed 3/2/2009, with respect to the rejection of claims 8-11 and 17-18 under 35 USC § 102(b) over Morain et. al. have been fully considered and are persuasive. In the office action dated 10/28/2008, claims 8-11 and 17-18 had been rejected under 35 USC § 102(b) as being anticipated by Morain et. al., Mol. Pharmacology, 46, pp. 732-742. The Applicants' traversal to this rejection was that the structure taught by Morain et. al. is different from the instantly claimed compounds. As claims 8-10 and 17-18 have been withdrawn, the rejection of these claims is considered moot, and the rejection as it was applied to instant claim 11 is discussed. Morain et. al. teaches a structure of the general formula shown below (p. 733, structure above Table 2):



For this structure, R=CF_3. The instant claims are drawn to a guanidine compound of formula I, which does share the same core structure as the compound taught by Morain et. al. However, the ring attached to the thiazole ring in the compound taught by Morain et. al. is an unsaturated benzene ring; the instant claims cite compounds in which this ring is saturated, except for the two double bonds of the thiazole ring. Therefore, it is acknowledged that the compound taught by Morain et. al. is different from the instantly

claimed compounds. The rejection of instant claim 11 under 35 USC § 102(b) over Morain et. al. is considered improper and is withdrawn.

5. In consideration of the new amended set of claims, a new art rejection over claims 11, 13-14, and 22-26 has been made, which will be discussed in detail further in this action. Previously, in the office action dated 10/28/2008, it had been stated by the examiner that the elected compound of formula I, N-[6-(3,4-dimethoxy-phenyl)-4,5,6,7-tetrahydro-benzothiazol-2-yl]-guanidine, was free of the prior art. The search has therefore been expanded to other species of formula I.

6. Claims 11-16, and 22-26 are pending.

7. Claims 11-16, and 22-26 were examined.

8. Claims 11, 13-14, and 22-26 were rejected.

9. Claims 12, and 15-16 are objected to.

Claim Rejections-35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

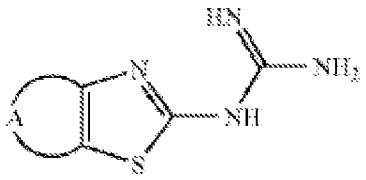
1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

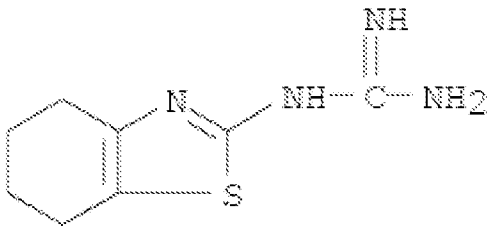
13. Claims 11, 13-14, and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ann. Rep. Takeda Res. Lab., 27, pp. 96-111, by Usui. A copy of this journal article has been requested, and a copy will be sent to the Applicants as soon as it is available. For convenience, an abstract of this reference was used for this rejection.

14. Instant claim 11 cites a compound of formula (I), and its pharmaceutically acceptable salts, of the structure shown below:



Where A=3 to 6 carbon chain, and A does not comprise double bonds; atleast one of A is substituted by one or more of methyl, etc. Instant claim 11 also cites pharmaceutically

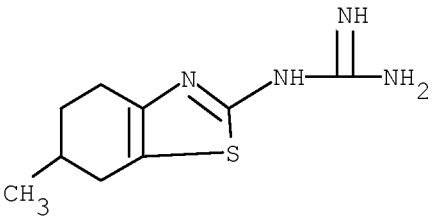
acceptable salts of formula (I). Usui discloses the compound, N-(4,5,6,7-tetrahydro-2-benzothiazolyl) guanidine, which has the structure shown below (Abstract):



The guanidine derivative taught by Usui has A=4 carbon chain.

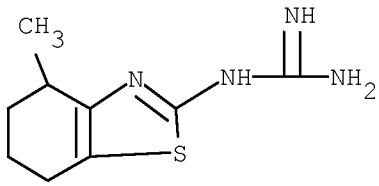
As substituent A of formula (I) in instant claim 11 consists of a 3-6 carbon chain, which is substituted with atleast one methyl group, etc., the instantly claimed compound is very similar to the compound disclosed by Usui. The only difference between the instantly claimed compound and the compound taught by Usui is that for the instant claim, ring A has atleast a methyl substituent; the guanidine derivative disclosed by Usui only has hydrogen substituents for ring A. However, the substitution of a hydrogen group for a methyl group would have been obvious for one of ordinary skill in the art, due to the structural similarities between the groups, and that the groups are homologues of each other. Therefore, the instantly claimed mono-methyl substituted compounds of formula I are obvious over the guanidine compound taught by Usui.

Instant claim 13 cites the compound, N-(5-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine. This compound is shown below:



In comparing the compound of instant claim 13 to the guanidine compound disclosed by Usui, the only difference is that for the instantly claimed compound, the 5-position of the ring has a methyl substituent; for the compound taught by Usui, this position is occupied by a hydrogen. However, the substitution of a methyl for hydrogen would have been prima facie obvious to one of ordinary skill in the art, as both groups are similar structurally and are homologous.

Instant claim 14 cites the compound, N-(7-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl—guanidine, which is shown below:



The compound cited in instant claim 14 differs from the guanidine compound taught by Usui by the substitution of a hydrogen group for a methyl at the 7-position of the ring. As discussed supra, such a substitution would have been obvious to one of ordinary skill in the art at the time of the invention. Additionally, it has been established that the substitution of a methyl group in place of a hydrogen is not patentable, in the absence of unexpected or unobvious results, *In re Lincoln*, 126 U.S.P.Q. 477, 53

U.S.P.Q. 40 (C.C.P.A. 1942); *In re Druey*, 319 F.2d 237, 138 U.S.P.Q. 39 (C.C.P.A. 1963); *In re Lohr*, 317 F.2d 388, 137 U.S.P.Q. 548 (C.C.P.A. 1963); *In re Hoehsema*, 399 F.2d 269, 158 U.S.P.Q. 598 (C.C.P.A. 1968); *In re Wood*, 582 F.2d 638, 199 U.S.P.Q. 137 (C.C.P.A. 1978); *In re Hoke*, 560 F.2d 436, 195 U.S.P.Q. 148 (C.C.P.A. 1977); *Ex parte Fauque*, 121 U.S.P.Q. 425 (P.O.B.A. 1954); *Ex parte Henkel*, 130 U.S.P.Q. 474, (P.O.B.A. 1960).

Instant claim 22 cites the compound as cited in instant claim 11, in a composition. Usui discloses that an HI salt of N-(4,5,6,7-tetrahydro-2-benzothiazolyl) guanidine is prepared from a solution comprised of ethanol and other compounds (Abstract, p. 1, last sentence). HI salts are known in the art as pharmaceutically acceptable. Therefore, Usui teaches that a pharmaceutically acceptable salt of the guanidine compound is present in a composition. As the methyl ring substituted derivatives of the guanidine compound are obvious derivatives of the hydrogen substituted compound, as discussed supra, Usui also teaches that the methyl ring substituted derivatives are present in compositions.

Instant claim 23 cites the compound of instant claim 11 in an inert carrier. Usui teaches that the HI salt of N-(4,5,6,7-tetrahydro-2-benzothiazolyl) guanidine is present in ethanol. Ethanol is known in the art as an inert carrier; therefore, Usui also teaches the limitations of instant claim 23.

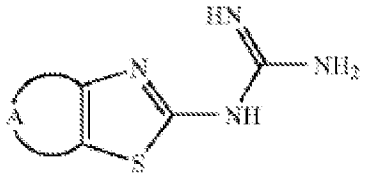
Claim Rejections-35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

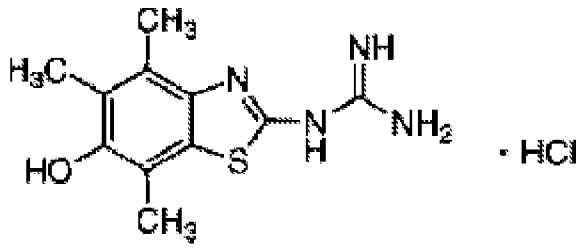
16. Claims 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 09-059258 application publication. The examiner would like to point out that claim 24 cites a compound of formula I, and that A=3 to 6 carbon ring. Additionally, it is cited that A, “together with the thiazole ring can form a cyclopentathiazole, benzothiazole,....,or thiazoloxepane skeleton which contains only the two double bonds of the thiazole component". Therefore, claim 24 has been interpreted to read that in addition to claiming structures of formula I in which A is saturated, compounds that have an unsaturated ring structure A, such as benzothiazole, are also included. Claims 25-26, which are dependent claims of claim 24, have been interpreted in the same manner.

17. Instant claim 24 cites a compound of formula (I) below:



Where A=3 to 6 carbon chain, and together with the thiazole ring can form benzothiazole, etc. Additionally, instant claim 24 cites that ring A has atleast one substituent that is methyl, etc., and also, that the compound of formula (I) includes pharmaceutically acceptable salts.

The JP 09-059258 publication (JP ‘258) discloses a compound of formula (148) shown below (p. 76, paragraph [0289]):



The ring A for the compound above is a 4 carbon chain.

The instant claim cites that A=3 to 6 carbon chain, and that A is substituted atleast in one position by CH_3. Compound of formula (148) of the JP ‘258 publication has methyl substituents at 3 positions, and has the same core structure as the instantly cited compound. Therefore, the compound cited in instant claim 24 is anticipated by the compound of formula (148), as taught by the JP ‘258 publication. The HCl salt is known in the art as a pharmaceutically acceptable salt (p. 10, paragraph [0031]).

Instant claim 25 cites a pharmaceutical composition comprising the compound of instant claim 24, and instant claim 26 cites the compound of claim 24 in an inert carrier. The JP ‘258 publication discloses that the guanidine compound of formula (148) is used to reduce the physiological occurrence of the Maillard reaction, thereby also reducing glycosylation of proteins that are associated with diabetes, and age related diseases (p. 4, paragraph [0003]-. 5, paragraph [0011]). The JP ‘258 also provides an example of a tablet form of the drug and other derivatives (p. 76, paragraph [0295]) with cellulose, therefore disclosing a pharmaceutical composition of the guanidine compound with an inert carrier.

Claim Objections

18. Claims 12 and 15-16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is

(571)270-7710. The examiner can normally be reached on Monday-Thursday 8:00 AM - 6:30 PM EST, with Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617